HYDROCODONE BITARTATE AND ACETAMINOPHEN - hydrocodone bitartrate and acetaminophen liquid

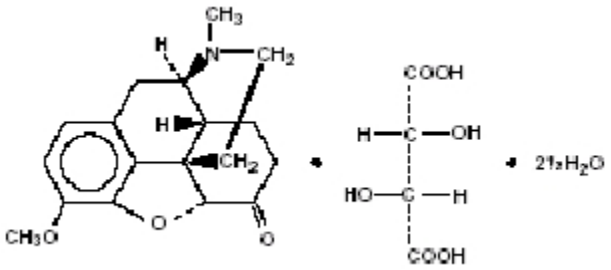
DESCRIPTION

Hydrocodone Bitartrate and Acetaminophen Elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate.....	1.67 mg	5 mg
(***WARNING:** May be habit forming)		
Acetaminophen.....	167 mg	100 mg
Alcohol.....	7%	7%

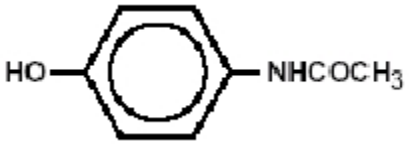
Also contains citric acid anhydrous, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, with FD&C Red #40 as coloring, and artificial flavoring.

Hydrocodone bitartrate is an opioid analgesic and antitussive which occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1) hydrate (2:5). Its structure is as follows:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\ 1/2\ H_2O$ M.W. 494.50

Acetaminophen, 4’-hydroxyacetanilide is a non-opiate, non-salicylate analgesic and antipyretic which occurs as white, odorless, crystalline powder possessing a slightly bitter taste. Its structure is as follows:



$C_8H_9NO_2$ M.W. 151.16

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

Radioimmunoassay techniques have recently been developed for the analysis of hydrocodone in human plasma. After a 10 mg oral dose of hydrocodone bitartrate, a mean peak serum drug level of 23.6 ng/mL and an elimination half-life of 3.8 hours were found.

The analgesic action of acetaminophen involves peripheral and central influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract, producing maximum serum concentrations within 30 minutes to one hour. The plasma half-life in adults and children ranges from 0.90 hours to 3.25 hours with an average of approximately *2* hours. The drug distributes uniformly in most body fluids and is approximately 25% protein bound. Acetaminophen is conjugated in the liver, with less than 3% of the dose excreted unchanged in 24 hours. The primary metabolic pathway is conjugation to sulfate and glucuronide by-products. A minor oxidative pathway forms cysteine and mercapturic acid. These compounds are subsequently excreted by the kidneys into the urine.

INDICATIONS AND USAGE

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS

Respiratory Depression
At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure
The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions
The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Special Risk Patients
As with any narcotic analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypetrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients
Hydrocodone Bitartrate and Acetaminophen Elixir, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Cough Reflex
Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Drug Interactions
Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.
The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.
The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy

Teratogenic Effects

Pregnancy Category C
Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7 to 1 mg/kg q6h, and paregoric 2 to 4 drops/kg q4h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosage decreased as tolerated.

Labor and Delivery
As with all narcotics, administration of Hydrocodone Bitartrate and Acetaminophen Elixir to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Hydrocodone Bitartrate and Acetaminophen Elixir, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down.
Other adverse reactions include:
Central Nervous System
Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.
Gastrointestinal System
The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of Hydrocodone Bitartrate and Acetaminophen Elixir may produce constipation.
Genitourinary System
Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.
Respiratory Depression
Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE
Hydrocodone Bitartrate and Acetaminophen Elixir is subject to the Federal Controlled Substances Act (Schedule III).
Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, Hydrocodone Bitartrate and Acetaminophen Elixir should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Hydrocodone Bitartrate and Acetaminophen Elixir is used for a short time for the treatment of pain. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Acetaminophen
Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.
In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.
The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Hydrocodone
Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle

flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.
Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration
An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.
Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION
Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should so kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.
The usual adult dosage is one or two tablespoonfuls (15-30 mL) every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

HOW SUPPLIED
Hydrocodone* Bitartrate and Acetaminophen Elixir is a pink-colored, strawberry-flavored liquid containing 5 mg of hydrocodone* bitartrate (***WARNING:** May be habit forming) and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied in bottles of 4 fl oz (118 mL), NDC
46672-584-04, in bottles of 16 fl oz (473 mL), NDC 46672-584-16, and in bottles of one gallon (3.785 L), NDC 46672-584-28.
Storage: Store at controlled room temperature 15-30°C (59-86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.
CAUTION: Federal law prohibits dispensing without prescription.
A Schedule III Controlled Substance.
Manufactured by:
MIKART, INC.
Atlanta, GA 30318
Rev. 5/91 Code 541Z00